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[KHIMIYA GETEROANALOGOV IZOFLAVONOV]

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CHEMISTRY OF ISOFLAVONE HETEROANALOGS*

1b** BENZOTHIAZOLE ANALOGS OF ISOFLAVONES

3-(2-Benzthiazolyl) chromones with electron-acceptor and electron-donor substituents as well as chromones not substituted in position 2 were produced through the interaction of α-(2-benzothiazolyl)-2,4-dihydroxy-5-alkylacetophenones and the anhydrides and chloranhydrides of carbonic acids. Their acylation, alkylation, aminoacylation reactions were studied as were their interactions with electrophilic and nucleophilic reagents.

The great amount of attention focused in recent years on the heterocyclic analogs of isoflavonoids is explained by the presence of general and specific types of biological action within them. Methods for synthesis of the imidazole [2], pyrazole [3], and isoxasole [4] analogs of isoflavones have been developed in view of the importance and the insufficient level of study accorded the azole analogs of isoflavones as potential physiologically active substances. As pharmacology tests have shown, some of these compounds exhibit high hypolipidemic, anti-inflammatory and sugar-reducing activity.

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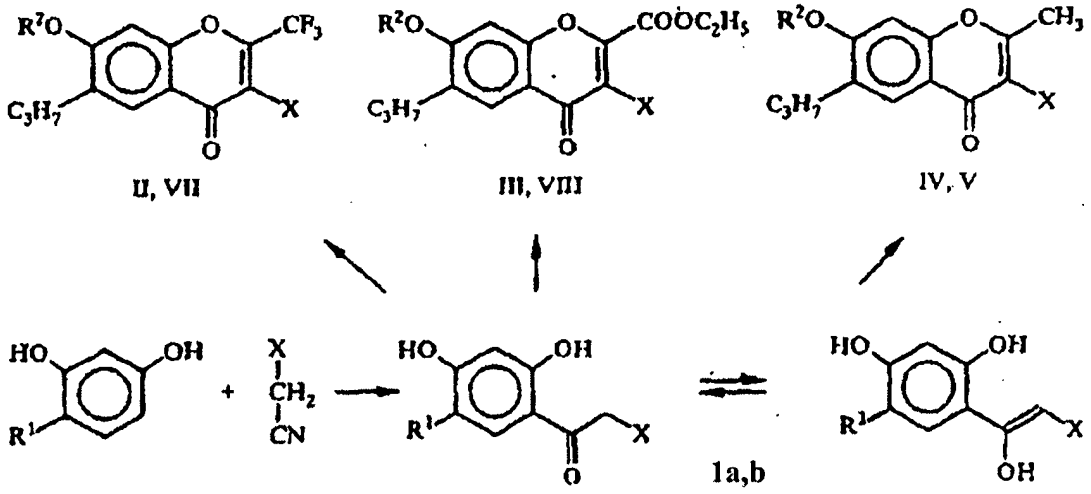
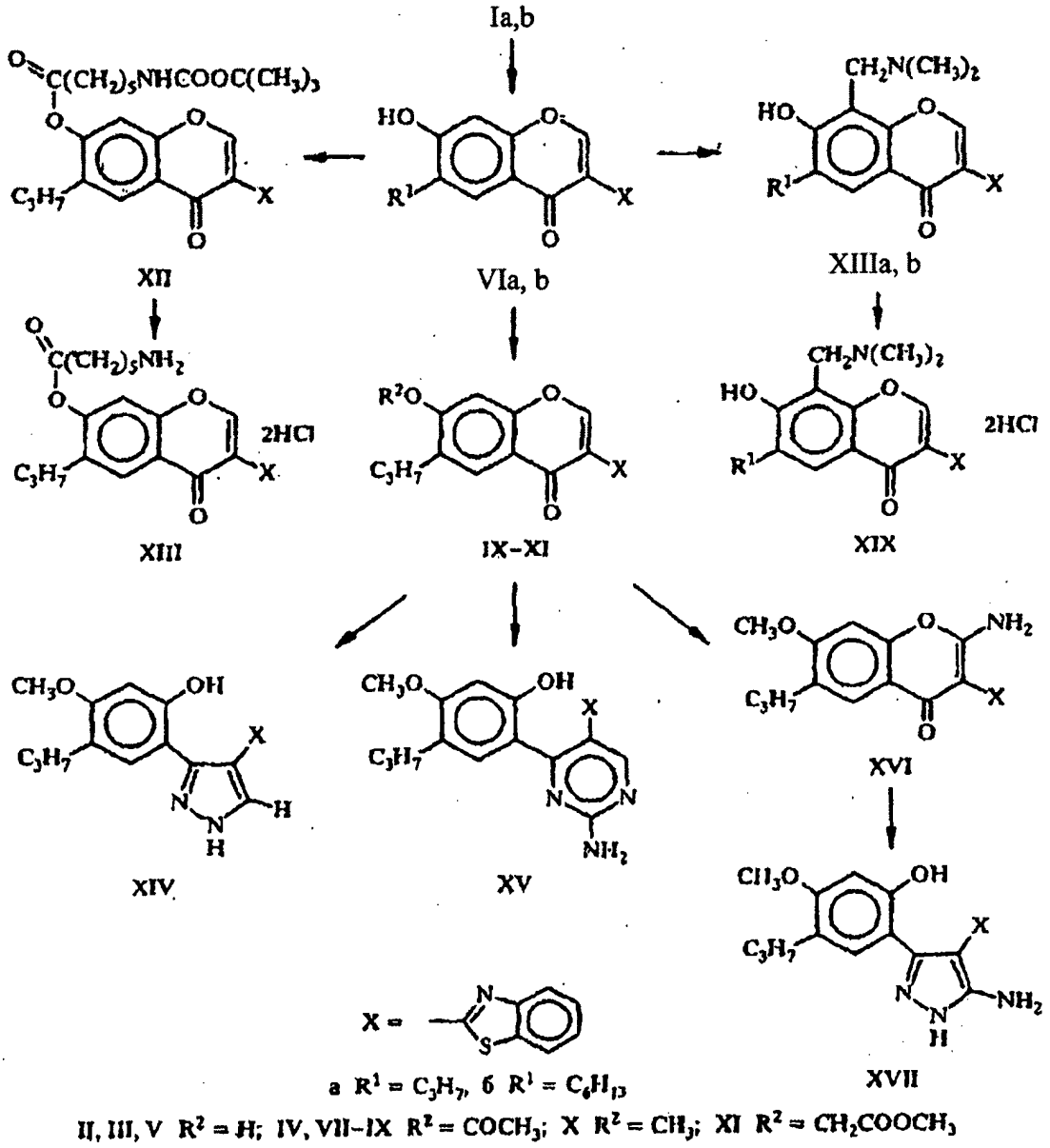
*Numbers in margin refer to pagination in original document.
** See report 15 [1].

Continuing the research into the field of the chemistry and pharmacology of chromones and nitrogen-containing heterocyclics, we have currently accomplished the synthesis and studied several properties of the benzothiazole analogs of isoflavones (see diagram) in the series of which, only two representatives have been described [5].

α-(2-Benzothiazolyl)-2,4-dihydroxy-6-propylacetophenone (1a) and α-2-benzothiazolyl)-2,4-dihydroxy-6-hexylacetophenone (1b) produced by condensation of 2-benzothiazolylacetonitrile with 4-alkylresorcins in modified conditions of the Gesh reaction served as the original compounds for synthesis of new 3-(2-benzothiazolyl)chromones.





Ketones Ia,b consist of high-melting yellow-colored crystal substances that produce a colored chelating complex with an alcohol solution of ferric chloride. The dark green color of this complex allowed us to assume the presence of tautomeric equilibrium between the ketone and enol forms for compounds Ia,b

in the solution. With analysis of the PMR spectrum of compound Ia indifferent deutero-solvents, we found that it exists exclusively in the ketone form in non-polar solvents such as chloroform and benzene and some quantity of the enol form is seen in the more polar acetone. Ketone Ia is enolized by 80% in dimethylsulfoxide, a fact to which the doubled number of proton signals from the hydroxyl groups and calculation of the integral intensity of unexchanged aromatic protons in the phenol component attest as does the reduction in the intensity of the peak of methyl chain protons, the appearance and increase in the intensity of the signal of the methane proton from the olefin fragment of the molecule (see figure). Ketone Ib is enolized by 85% in dimethylsulfoxide. The high level of the enol form is possibly associated with its stabilizing intermolecular hydrogen bond occurring between the enol hydroxyl and dimethylsulfoxide.

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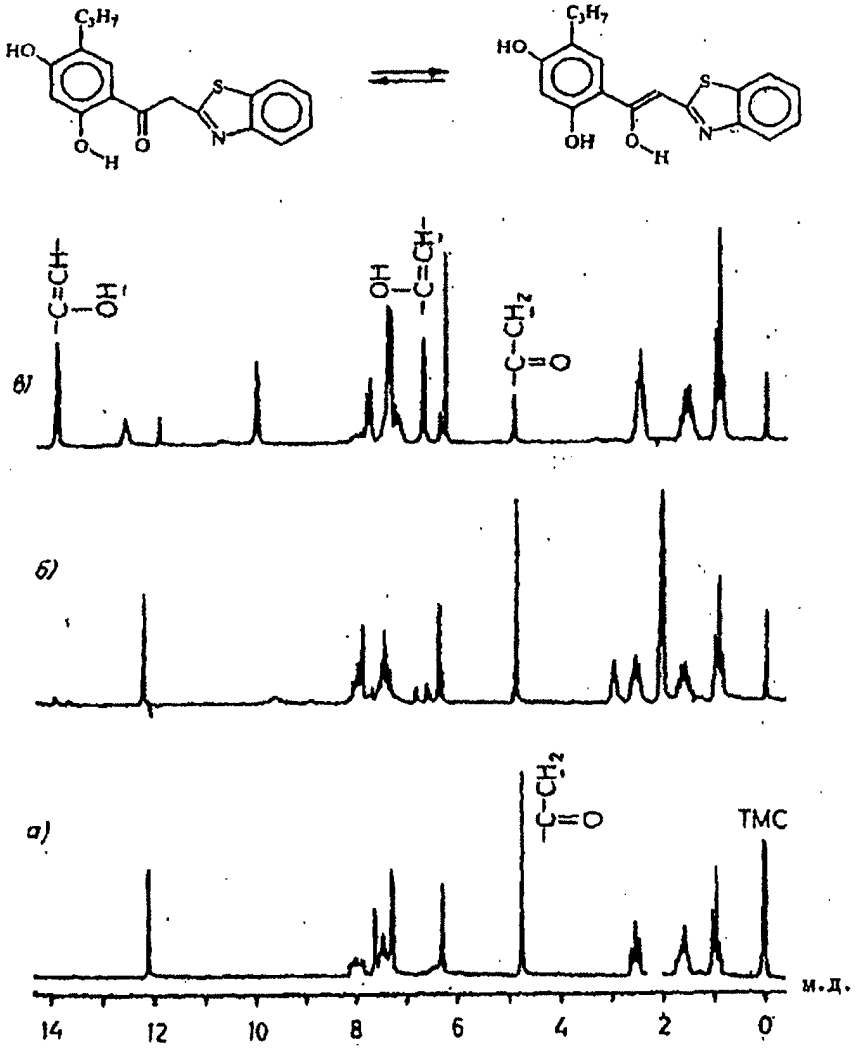
Chromones II and III, which contain trifluoromethyl and ethoxycarbonyl groups in position 2, respectively, are produced as a result of the interaction of ketone Ia and trifluoroacetic anhydride or ethoxyalyl chloride in pyridine in the cold. The reaction of acetic anhydride with this ketone occurs in a pyridine medium at room temperature with the formation of 2-methyl-7-acetoxychromone IV; hydrolysis of the latter in an alkaline medium leads to 2-methyl-7-hydroxychromone V. The

realization of cyclization in soft conditions attests to the increased activity of the α-methylene chain of ketone Ia, which is brought about by the electron-acceptor properties of the benzothiazole cycle.



PMR spectrum of α-(2-benzothiazolyl)-2,4-dihydroxy-5-propyl-acetophenone: *a*- in deuterochloroform; *b*- in teruteroacetone; *c*- in deuterodimethyldulfoxide.
Translator's note: Russian letters "m.d." at far right side of x axis stand for "dislocation point" [English abbreviation d.p.].

It was possible to use the Venkataraman method as was shown previously [5] in the example of the benzothiazole isoflavone analog to produce 3-(2-benzothiazolyl) chromones VIa,b that do not contain substituents in position 2 of the chromone system. However, having noted the results of references [6 - 8] and the nature of ketones 1a,b, we decided to study the conditions of their cyclization in chromones VIa, b under the influence of acetic-formic anhydride. As it happened, the use of this convenient and effective reagent made it possible to carry out cyclization even in the absence of a base and to obtain a high-quality target product that does not require further purification.

In contrast to the original ketones Ia,b, signals from the methylene chain and 2-OH group are absent in the PMR spectra of chromones II-VI. In addition, the presence of 2-H proton signals of the methyl and ethoxyl group in the PMR spectra of these compounds as well as the negative reaction with an alcohol solution of ferric chloride attest to the completeness of the conversion of ketones Ia,b and the corresponding chromones (see table).

The benzothiazole analogs of isoflavones II, III, V and VI that we synthesized are readily acylated through the phenol hydroxyl. The action of acetic anhydride in pyridine solutions

of these compounds at room temperature leads to formation of the corresponding 7-acetoxy- derivatives of IV, VII-IX, which are converted quantitatively to the corresponding 7-hydroxychromones II, III, V, VI under the influence of a 5% solution of NaOH. Methylation through the 7-OH group of the chromone cycle occurs smoothly when chromone VIa is processed with dimethylsulfate in an acetone solution in the presence of potash, which leads to chromone X. Alkylation with the methyl ester of monobromoacetic acid also occurs readily in a dioxane solution in the presence of potash with formation of 7-O-methoxycarbonyl methoxychromone XI. It was not possible to carry out alkylation of the same chromone VIa through the nitrogen in the benzothiazole ring in a boiling dioxane solution with the same reagent but without potassium.

Aminoacyl derivative XII, whose subsequent acetolysis leads to the hydrochloride of 3-(2-benzothiazolyl)-7-(6-amino-caproyl)oxy-chromone XIII, was produced as a result of the condensation of chromone VIa with N-tert-butyloxycarbonyl-6-amninocaproic acid in a medium of tetrahydrofuran in the presence of dicyclohexyl-carbodiimide.

The structure and individual nature of the re-synthesized 7-substituted chromones IV, VII-XII were confirmed by data from elemental analysis, thin-layer chromatography and PMR spectroscopy (see table).

It was also of interest to produce peptide derivatives through the 2-carboxyl group of chromones and for this reason, we attempted to carry out saponification of the complex-ester group of chromone III. In the process of boiling chromone III in a water-alcohol medium with an equivalent quantity of 5% NaOH, however, saponification did not occur and in the process of boiling with a larger quantity of the alkali, chromone III broke down to ketone Ia, to which the appearance of a positive reaction with an alcohol solution of ferric chloride will attest. Chromone III behaves similarly in a water-alcohol solution of soda. Saponification of the complex-ester group does not occur even when chromone III is boiled in a water-alcohol solution with double the quantity of hydrochloric acid for a period of 6 hours. Looking at the results in reference [9], we heated chromone IV in concentrated hydrochloric acid. After crystallization from ethyl acetate and the dimethyl-formamide that precipitated from the reaction medium of the product, the latter was identified as chromone VI not substituted at position 2, that is, saponification of the complex-ester group did not take place but rather, there was complete decarboxylation. The identical nature of its IR and PMR spectra to the spectra of base chromone VI, their identical R_f on the thin-layer chromatography plates and the absence of depression when measuring the melting temperature of the mixed

sample can serve as confirmation of the compound that was produced.

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Characteristics of the (3-(2-benzothiazolyl) chromones III-XIII, XVI, XVIII

Compound	Gross-formula	T_{mel} °C	PMR spectrum, δ, point of dislocation*						Yield, %
			Protons of chromone cycle					Benzothiazol protons	
			2-R	5-H	6-AR	7-R	8-R		
III	$C_{22}H_{19}NO_5S$	245...247	4,47 1,24	7,92	0,93; 1,64; 2,65	11,31	7,02	8,20 (4-H); 7,52 (5-, 6-H); 8,00 (7-H)	75
IV	$C_{22}H_{19}NO_4S$	167...168	3,04	8,19	0,97; 1,68; 2,64	2,39	7,29	8,02 (4-, 7-H); 7,44 (5-, 6-H)	87
V	$C_{20}H_{17}NO_3S$	278...279	2,97	7,82	0,91; 1,59; 2,61	10,95	6,91	8,07 (4-, 7-H); 7,47 (5-, 6-H)	70
VIa	$C_{19}H_{15}NO_3S$	280...282	9,33	7,90	0,94; 1,63; 2,64	11,11	6,99	8,18 (4-H); 7,42 (5-H); 7,62 (6-H); 8,03 (7-H)	98
VIb	$C_{22}H_{21}NO_3S$	267...268	9,33	7,90	0,94; 1,65; 2,65	11,05	7,00	8,15 (4-H); 7,48 (5-, 6-H); 8,03 (7-H)	97
VII	$C_{22}H_{16}F_3NO_4S$	108...110	–	8,13	0,97; 1,68; 2,66	2,40	7,45	8,05 (4-, 7-H); 7,50 (5-, 6-H)	85
VIII	$C_{24}H_{21}NO_6S$	165...168	4,51 1,34	8,20	0,97; 1,70; 2,65	2,39	7,39	7,98 (4-, 7-H); 7,44 (5-, 6-H)	80
IX	$C_{21}H_{17}NO_4S$	220...222	9,25	8,25	0,98; 1,69; 2,65	2,39	7,37	8,01 (4-, 7-H); 7,45 (5-, 6-H)	72
X	$C_{20}H_{17}NO_3S$	202...204	9,19	8,08	0,97; 1,67; 2,63	3,94	6,89	7,97 (4-, 7-H); 7,45 (5-, 6-H)	80
XI	$C_{22}H_{19}NO_4S$	225...226	9,20	8,14	0,99; 1,68; 2,77	3,84 4,77	6,78	8,02 (4-, 7-H); 7,44 (5-, 6-H)	78
XII	$C_{30}H_{34}N_2O_6S$	165	9,20	8,25	0,98; 1,60; 2,70	*2	7,38	8,01 (4-H); 7,46 (5-, 6-H); 8,01 (7-H)	56
XIII	$C_{25}H_{28}Cl_2N_2O_4S$	286	9,47	8,14	0,92; 1,61; 2,71	*3	7,60	8,14 (4-, 7-H); 7,50 (5-, 6-H)	95
XVI	$C_{25}H_{18}N_2O_3S$	308...310	9,46 10,87	7,83	0,93; 1,61; 2,65	3,95	6,96	8,01 (4-, 7-H); 7,42 (5-, 6-H)	90
XVIIIa	$C_{22}H_{22}N_2O_3S$	125...126	9,21	7,80	0,92; 1,60; 2,57	8,77	4,08 2,46	8,05 (4-, 7-H); 7,47 (5-, 6-H)	77
XVIIIb	$C_{25}H_{28}N_2O_3S$	137...138	9,16	7,75	0,83; 1,26; 1,49; 2,41	10,48	4,04 2,41	8,13 (4-H); 7,43 (5-, 6-H); 7,98 (7-H)	70

* PMR spectra for compounds III, V, VIa, b, XII, XIII, XVI measured in DMSO-D6 and that for compounds IV, VIII-XI measured in $CDCl_3$

*2 $(CH_3)_3C$-O-CO-NH-$(CH_2)_5$COO – 1.46; 4.52; 2.65; 1.70; 3.17

*3 H_3N^+ - $(CH_2)_5$COO – [3].00; 2.71; 1.61; 2.71

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We also studied the interaction of 7-methoxychromone X with bifunctional nucleophilic reagents. Under the influence of hydrazine hydrate and aminoguanidine, 7-methoxychromone X undergoes recyclization into a derivative of pyrazole XIV and pyrimidine XV. The structure of these products was confirmed by means of chemical reactions and spectral data. Pyrazole XIV and pyrimidine XV dissolve in aqueous solutions of alkalis and produce a positive reaction with ferric chloride, which points

to the presence of molecules of a free hydroxyl group in them located near the nitrogen atom of the pyrazole or pyrimidine cycles. Diamagnetic shifts around dislocation point 1 of proton 6-H of the phenol fragment of pyrazone and pyrimidine attests to the occurrence of a reaction with disclosure of the pyrone cycle in comparison with the corresponding signal in original compound X. Protons of the OH and NH groups are seen in the PMR spectrum for pyrazole XIV in the form of an amplified singlet at 9.7 and 13.2, respectively and a 2-OH group is seen as a singlet at 10.2 and an amino group is seen at d.p. 7.3 in the PMR spectrum for pyrimidine XV.

In the reaction with hydroxylamine, chromone X undergoes double recyclization ending with the formation of 2-amino chromone XVI. The structure of the latter agrees with data from PMR spectroscopy. An amino group is seen with two signals at the 9.5 and 10.9 dislocation points, which points to its involvement in the formation of an intra-molecular hydrogen bond with an atom of nitrogen in the benzothiazole nucleus. Chemical shifting of proton 5-H of the chromone cycle is seen in the same area as in the original compound and attests to preservation of the pyrone structure in compound XVI. Data from IR spectroscopy ($\nu_{C=O}$ 1645, ν_{NH2} 3235, 3065 cm^{-1}) also argue in favor of an amino-chromone structure. There is a nitrogen atom in the amino group

in the spectrum ^{15}N NMR (it appears as a triplet at 95.0 d.p. with $J_{N,H}$ 90.33 Hz in nitromethane).

Under the influence of hydrazine hydrate, the 2-amino-chromone XVI recycles to 5-aminopyrazole XVII, which forms a complex that is blue-green in color with an alcohol solution of ferric chloride. In the PMR spectrum of this compound, signals relating to the protons of the hydroxyl and amino groups, and the 1-H proton of the pyrazole cycle are seen confirming the pyrazole structure of the product of recyclization. In the ^{15}N NMR spectrum of compound XVII, the atom of nitrogen in the amino group is seen at 50.8 d.p and as a triplet with $J_{N,H}$ 82.4 Hz. Electrophilic substitution in the series of benzothiazole analogs of isoflavones was studied in the example of the aminomethylation reaction. The reaction of chromones VIa, b with bisdimethylaminomethane in a dioxane medium while being heated leads to the formation of Mannich bases XVIIIa,b. The dimethyl-aminomethyl group enters position 8 of the chromone cycle to which the disappearance of the proton 8-H signal of the chromone cycle in the PMR spectrum and the appearance of signals that correspond to methylene protons and the protons of dimethylamino groups attest. As it passes through dry hydrogen chloride into the solution of chromone XVIIIa in dry chloroform, sediment of the corresponding chlorhydrate of XIX whose

composition is confirmed by data of elemental analysis is released.

Experimental Component

The occurrence of reactions and the purity of the compounds were monitored using the method of thin-layer chromatography on plates of Silufol UV-254; the eluents were mixtures of chloroform-methanol, benzene-ethanol (9:1) and ethyl acetate for the Mannich bases. Spectra of NMR^{1}H were recorded on Bruker WP-100SY and Bruker CXR-200 devices with respect to TMC (internal standard) while NMR^{15}N spectra were measured on a Bruker CXP-200 device with respect to nitromethane (internal standard). The infra-red spectra were determined in tablets of potassium bromide on a Rye Unicam SP-3-300 instrument.

Data from elemental analysis of new compounds in S, N and Cl correspond to calculations.

α-(2-Benzothiazolyl)-2,4-dihydroxy-5-propylacetophenone (Ia, $C_{18}H_{17}NO_3S$). Dry hydrogen chloride was passed through a mixture of 8.7 grams (50 mmol) 2-benzothiazolyl acetonitrile and 8.8 grams (5) mmol of 4-propylresorcin in 80 ml of boron trifluoride etherate while being stirred and heated to 60°C for a period of 10 - 12 hours. The reaction mixture was then added to 500 ml of hot water, boiled for 1.5 hours and neutralized

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with a solution of alkali to a pH of 7. After cooling, the sediment was filtered and thoroughly rinsed with water. The yield of raw product was 17 grams. Purification was carried out by re-sedimentation from an alkali solution and crystallization from alcohol. Yield was 12 grams (73%). Yellowish crystals with a T_{melt} of 175°C. PMR spectrum ($CDCl_3$): protons of the phenol component: 12.08 (2-OH); 6.28 (3-H); 8.5 (4-OH); 0.95; 1.58; 2.53 (5-C_3H_7); 7.60 (h-H); 4.73 (-Ch_2-); protons of benzothiazole: 8.01 (4-H); 7.44 (5-, 6-H); 7.89 d.p. (7-H). PMR spectrum (DMSO-D_6): protons of phenol component for the ketone form: 11.92 (2-OH); 6.37 (3-H); 10.69 (4-OH); 0.92: 1.55: 2.47 (5-C_3H_7); 7.82 (6-H); 4.94 (-CH_2-); protons of phenol component for the enol form: 12.57 (2-OH); 6.27 (3-H); 10.00 (4-OH); 7.34 (6-H),13.91; 6.71 (-C(OH)-CH-); protons of benzothiazole: (4-, 7-H); 7.35 d.p. (5-, 6-H). IR spectrum, $\nu_{C=O}$ 1643, ν_{OH} 3060, 3400 cm^{-1}).

α-(2-Benzothiazolyl)-2,4-dihydroxy-5-hexylacetophenone (16, $C_{21}H_{23}NO_3S$). Produced analogously to compound 1a from 8.7 grams (50 mmol) of 2-benzothiazolylacetonitrile and 10.1 grams (51 mmol) of 4-hexylresorcin. Yellowish crystals with a T_{melt} of 154 - 156°C. Yield of 5.5 grams (30%). PMR spectrum (DMSO-D_6); protons of phenol component for the ketone form: 11.90 (2-OH); 6.36 (3-H):10.68 (4-OH); 0.92; 1.34: 2.50 (5-C_6H_{13}); 7.80 (6-H); 4.92 (-CH_2); protons of phenol component for enol form: 12.57

(2-OH; 6.25(3-H); 9.99 (4-OH); 0.90; 1.34; 1.52; 2.59 (5-C_6H_{13}): 7.30 (6-H); 13.87: 6.68 (-C(OH)-CH-); protons of benzothiazole: 7.9 (4-, 7-H); 7.35 d.p. (5-, 6-H).

2-Trifluoromethyl-3-(2-benzothiazolyl)-6-propyl-7-hydroxy-chromone (II). Trifluoroacetic anhydride in an amount of 2.8 ml (20 mmol) was added drop by drop to a solution of 3.27 (10 mmol) ketone Ia in a minimum volume of pyridine as it was cooling. After 48 hours of standing at room temperature, the reaction mixture was decanted into 100 ml of water and the sediment that had precipitated was filtered. The compound was identified as acetyl derivative VII.

2-Ethoxycarbonyl-3-(2-benzothiazolyl)-6-propyl-7-hydroxy-chromone (III). Produced analogously to compound II from 10 mmol ketone 1a and 20 mmol of ethoxalylchloride and purified by crystallization from alcohol.

2-Methyl-3-(2-benzothiazolyl)-6-propyl-7-acetoxychromone (IV). Acetic anhydride in an amount of 10.2 grams (100 mmol) was added to a solution of 6.54 grams (20 mmol of ketone Ia in a minimal amount of absolute pyridine and the reaction mixture was left overnight at room temperature and at that point, the sediment was filtered, rinsed with cold water and crystallized from hexane.

2-Methyl-3-(2-benzothiazolyl)-6-propyl-7-hydroxychromone (V). Four (4) ml of a 5% solution of caustic soda was added to a

solution of 1.9 grams (4.8 mmol) of compound IV in 50 ml of alcohol. After several seconds, the boiling solution was diluted with water, boiled for 5 minutes and neutralized with diluted hydrochloric acid to a pH of 7; the sediment that had precipitated was filtered out and crystallized from alcohol.

3-(2-Benzothiazolyl)-6-alkyl-7-hydroxychromones(VIa,b). A mixture of 10 mmol of ketone 1a or 1b and 10 ml of acetic-formic anhydride was mixed for a short period time and then heated at 80-100°C for a period of 1-1.5 hours; after cooling, the reaction mixture of sediment was filtered and rinsed with cold alcohol. Compound VIa was crystallized from propyl alcohol and VIb was crystallized from alcohol.

3-(2-Benzothiazolyl)-6-propyl-7-acetoxychromones (VII, VIII, IV, IX). Acetic anhydride in an amount of 5 ml was added to a solution of 1 mmol of the corresponding 7-hydroxychromone in a minimal amount of pyridine and the reaction mixture was left to stand for a day at room temperature. The sediment that precipitated was filtered, rinsed with cold alcohol and crystallized from hexane (VII) or from acetic anhydride (VIII, IX).

3-(2-Benzothiazolyl)-6-propyl-7-alkoxychromones(X, XI). Dimethylsulfate in an amount of 1.14 ml (12 mmol) or the methyl ester of monobromoacetic acid in an amount of 1.33 ml (12 mmol) was added to a hot mixture of 3.37 grams (10 mmol) 7-hydroxychromone VIa and 4.1 grams (30 mmol) of potash in absolute

dioxane and boiled for 4 to 10 hours; inorganic sediment was filtered from the hot solution, the solvent was distilled off and compound X was crystallized from ethyl acetate while compound XI was crystallized from DMFA.

3-(2-Benzothiazolyl)-6-propyl-7-O-(N-tertbutyloxycarbonyl-6-aminocaproyl)chromone (XII). One (1) gram (0.5 mmol) of dicyclohexylcarbodiimide was added to a solution of 2.3 grams (10 mmol) of N-tertbutyloxycarbonyl-6-aminocaproic acid in 20 ml of tetrahydrofuran cooled to 0°C. The reaction mixture was mixed for 1 hour at 0°C. The dicyclohexylurea that precipitated was filtered off, 1.3 grams (4 mmol) of chromone VI and 12 mg (0.01 mmol) of N,N-dimethylaminopyridine was added to the filtrate. The resulting solution was stirred at room temperature for 2 hours, the solvent was distilled off in a vacuum, the residue was dissolved in 300 ml of ethyl acetate and then rinsed with 50 ml of water, a saturated solution of sodium bicarbonate (2 x 50 ml), 50 ml of water, with a saturated solution of sodium chloride (2 x 50 ml). The organic phase was dried with anhydrous magnesium sulfate, the solvent was distilled off in a

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vacuum, and the residue was recrystallized from methanol.

3-(2-Benzothiazolyl)-6-propyl-7-O-(6-aminocaproyl)-oxychromone chlorhydrate (XIII). A suspension of 1 gram of compound XII in 50 ml of ether saturated with hydrogen chloride

was stirred for 1 hour and the sediment was filtered off. It was purified by re-precipitation with ether from a methanol solution.

3-(2-Hydroxy-4-methoxy-5-propylphenyl)-4-(2-benzothiazolyl) pyrazole (XIV, $C_{20}H_{19}N_3O_2S$). An alcohol solution of hydrazine anhydrate was added to a solution of 0.7 grams (2 mmol) of chromone X in 25 ml of alcohol and the reaction mixture was heated for 5 - 10 minutes. Yellow coloration appeared which disappeared at the end of the reaction. After diluting the solution with water, the sediment was filtered and crystallized from alcohol. Yield was 0.5 grams (90%). Colorless crystals with T_{melt} = 247°C. PMR spectrum (DMSO-D_6): protons of the phenol component: 9.72 (2-OH); 6.59 (3-H); 3.81 (4-OCH_3);l 0.87: 1.52; 2.45 (5-C_3H_7); 7.06 (6-H); protons of pyrazole: 13.2 (N-H); 8.13 (5-H); protons of benzothiazole: 7.92 (4-, 7-H); 7.29 (5-H); 7.44 d.p. (6-H).

2-Amino-4-(2-hydroxy-4-methoxy-5-propylphenyl)-5-(2-benzo-thiazolyl)pyrimidine (XV, $C_{21}H_{20}N_4O_2S$). Guanidine hydrochloride in an amount of 1.91 grams (0.02 mol) was added to a solution of 0.92 grams (0.04 mol) of sodium in 50 ml of absolute alcohol and the sediment of sodium chloride was filtered off after 5 minutes. Chromone X was added to the resulting filtrate and the reaction mixture was boiled for 20 hours. The dry residue was diluted in 100 ml of cold water after evaporation of the alcohol

in a vacuum and acidified with dilute hydrochloric acid to a pH of 6. The product that precipitated was filtered and crystallized from alcohol. Yield was 2.9 grams (75%). Yellowish crystals with T_{melt} of 236-238°C. PMR spectrum (DMSO-D_6): protons of the phenol component: 10.17 (2-OH); 6.42 (3-H); 3.77 (4-OCH_3); 0.87: 1.53; 2.45 (5-C_3H_7): 6.95 (6-H); protons of the pyrimidine cycle: 7.30 (2-NH_2); 8.85 (6-H); protons of benzothiazole; 7.95 (4-, 7-H); 7.39 d.p. (5-, 6-H).

2-Amino-3-(2-benzothiazolyl)-6-propyl-7-methoxychromone (XVI). A mixture of 0.35 grams (1 mmol) of chromone X, 0.2 grams (3 mmol) of hydrochloric acid hydroxylamine and 2 ml of absolute pyridine were heated at 100 - 120°C for 3 hours. The sediment was filtered off and crystallized from dimethylformamide.

3-(2-Hydroxy-4-methoxy-5-propylphenyl)-4-(2-benzothiazolyl)-5-aminopyrazole (XVII, $C_{20}H_{20}N_4O_2S$) was produced analogously to compound XIV from 0.73 grams (2 mmol) of chromone XVI in alcohol and 12 ml of a 2 n alcohol solution of hydrazine anhydrate by boiling 5-10 minutes and purifying by crystallization from alcohol. Yield was 0.58 grams (78%). Colorless crystals with a T_{melt} of 236-238°C. PMR spectrum (DMSO-D_6): protons of the phenol component: 9.46 (2-OH): 6.58 (3-H); 3.81 (4-OCH_3); 0.88; 1.53; 2.46 (5-C_3H_7): 6.94 (6-H); protons of

pyrazole: 12.03 (N-H); 5.7 (5-NH_2); protons of benzothiazole: 7.85 (4-H); 7.32 (5-, 6-H); 7.85 d.p. (7-H).

3-(2-Benzothiazolyl)-6-alkyl-7-hydroxy-8-dimethylamino-methylchromone (XVIIIa,b). A mixture of 5 mmol of the corresponding chromone VIa or VIb and 2.5 ml of bisdimethylaminomethane in 25 ml of absolute dioxane were boiled for 1.5 to 2 hours. The dioxane and excess amine were distilled off at reduced pressure and XVIIIa was crystallized from hexane while XVIIIb was crystallized from alcohol.

Chlorhydrate of 3-(2-benzothiazolyl)-b-propyl-7-hydroxy-8-dimethylaminomethylchromone (XIX). Mannich base XVIIIa was dissolved in dry chloroform and passed through dry HCL until the formation of sediment had stopped. The sediment was filtered and dried. Yield was quantitative.

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